

## **REMARKS/ARGUMENTS**

Claims 23-35, and 64-79 are pending. Claims 23-35, 64 and 65 are amended. New claims 66-79 are added.

### **1 Novelty and Nonobviousness of the Claimed Invention**

The striking and unexpected results demonstrated by applicants, e.g., at page 47 of the application, reveal an invention that opens an entire new avenue of drug development in the area of central nervous system therapeutics that traverse the blood-brain barrier. The data presented by the applicants illustrates that the conjugation using the applicants claimed invention resulted in central nervous system delivery and that the activity was present for an extended period of time. Nothing in Ekwuribe et al.<sup>1</sup> teaches or suggests that the compounds described therein (the “Ekwuribe compounds”) can be administered to a subject and thereafter traverse the blood-brain barrier to enter the central nervous system and activate a receptor.

A skilled artisan might be motivated to administer the Ekwuribe compounds peripherally to induce a peripheral effect. However, one skilled in the art would not be motivated to administer the Ekwuribe compounds peripherally in order to induce an effect that is mediated in the central nervous system. Alternatively stated, a skilled artisan *would not be motivated to select a subject in need of an effect mediated in the central nervous system for a peripheral administration of the Ekwuribe compounds.* Nothing in Ekwuribe et al. or in the remaining references cited by the Examiner suggests such selection.

Claim 23 has been modified to emphasize this aspect of the invention. The claim now requires activation of “a central nervous system receptor in a subject in need of an effect mediated in the central nervous system,” and further requires that the “the conjugate traverses the blood-brain barrier of the subject to come into contact with and activate the receptor and thereby produce the effect.” This amendment is supported, inter alia, by the data reproduced above, as well as in the example provided in Section 5.8, which empirically demonstrates peripheral administration followed by traversal of the blood-brain barrier, and in the example provided in Section 5.9 of the specification showing binding to receptors in brain sections, and at page 4, line 11, where the specification states:

There is therefore a need for pharmaceutical compositions which can ... penetrate through the BBB in sufficient amounts and at sufficient rates to be efficacious.

See also page 6, line 4, stating:

There is therefore a need in the art for means for enabling therapeutic agents, such as peptides, to cross the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce the desired therapeutic effect.

Other support can be found throughout the specification (e.g., p. 18, lines 3-7, p. 34, lines 4-9), and indeed, the amendment is in line with the entire thrust of the application.

In conclusion, the applicants' amendment to claim 23 overcomes the rejections made under 35 USC §§ 102 and 103(a), and the Examiner is respectfully requested to withdraw these objections.

## **2 Resolution of Issues Under 35 USC § 112**

The Examiner proposed modifying claim 24 to replace "characterized in that" with "wherein." The applicants have made this amendment. The Examiner also pointed out a typographical error in claim 24 ("activity the without"), and the applicants have revised the wording in question to read "activity in the central nervous system without," which obviates the typographical error.

The examiner noted further that in claim 33, the Markush group is directed to peptides, but not all members are peptides. The applicants have removed reference to peptides in the preamble of the Markush group to alleviate this inconsistency.

The foregoing amendments overcome the rejections to claims 24 and 33 based on 35 USC § 112, and the Examiner is therefore respectfully requested to withdraw these rejections.

## **3 Other Amendments and New Claims**

Claims 25-35 and 64-65 are amended to clarify that these claims depend from claim 23, to make the claims consistent with the numbering used by the Examiner in the Office Action.

New claims 66-72 are added to separate the formulae originally found in claim 33 into individual dependent claims depending from claim 23.

New claims 73 and 74 are added to emphasize the aspect of the invention in which the conjugate is administered parenterally (claim 73) and orally (claim 74).

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<sup>1</sup> The Examiner cited Ekwuribe, US Patent 5,681,811 as the basis for a rejection under 35 USC §§ 102 and 103(a).


Finally, new claims 75-79 are added to emphasize the aspect of the invention in which activation of the receptor induces analgesia in the subject.

#### 4 Conclusion

The pending claims are now in condition for allowance. In the event that any issues remain incident to formal allowance of the application, the Examiner is requested to contact the undersigned attorney at (919) 286-8104.

Dated: 1-28-05

Respectfully submitted,

By:   
William A. Barrett  
Registration No. 42,296  
Attorney for Applicants